Long-Term Safety and Efficacy of Tralokinumab in more than 1400 Patients with Moderate-to-Severe Atopic Dermatitis Treated for up to 42 Months: an Interim Analysis of ECZTEND

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Introduction

- Atopic dermatitis (AD) is a chronic and debilitating inflammatory skin disease requiring long-term treatment options with a favorable safety profile[1,2]
- As we gain a better understanding of the immune process underlying AD, more targeted treatment options are being developed to improve long-term efficacy and safety
- In the skin, interleukin (IL)-13 is a major driver of immune dysregulation, skin barrier dysfunction, and microbiome dysbiosis, which characterize AD[3–6]
- Tralokinumab, a first-in-class, fully human monoclonal antibody, specifically neutralizes IL-13 with high affinity[7]
- Phase 3 studies with tralokinumab have demonstrated favorable safety and sustained efficacy in adult patients with AD for up to 1 year[8,9]
- Given the chronic nature of AD, long-term treatment options are needed with a favorable safety profile[10]
- An ongoing extension trial, ECZTEND (NCT03587805), is assessing the safety and efficacy of treatment with subcutaneous tralokinumab 300 mg every 2 weeks (Q2W) following participation in a parent trial (PT)

Objective

- To assess the safety and efficacy of long-term tralokinumab treatment for adults with moderate-to-severe atopic dermatitis

Methods

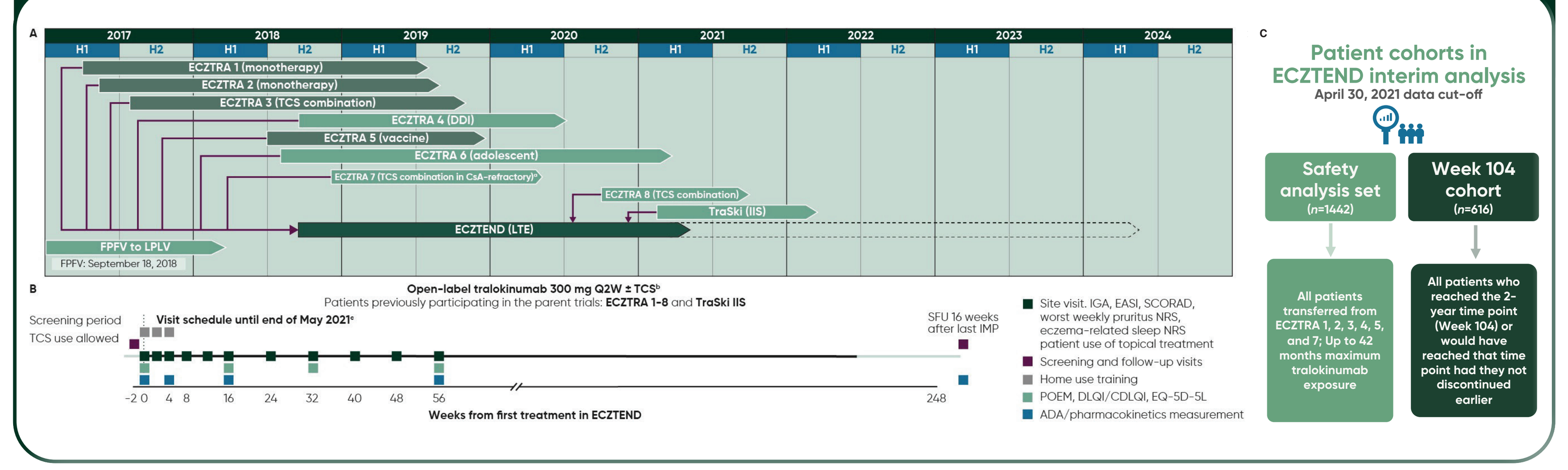
Study design (Figure 1)

- ECZTEND is an open-label, 5-year extension trial including adult and adolescent patients with AD in 11 countries who previously participated in the tralokinumab PTs ECZTRA 1–8[8,9] or the TraSki investigator-initiated study (IIS) **(Figure 1A)**
- In ECZTEND, patients received open-label tralokinumab 300 mg Q2W (home use) plus optional topical corticosteroids (TCS), with visits every 8 weeks **(Figure 1B)**
- Data are presented from 1442 eligible adult patients with moderate-to-severe AD from multinational clinical trials of tralokinumab completed at data cut-off (April 30, 2021; ECZTRA 1, 2, 3, 4, 5, and 7). Patients received up to 42 months of total tralokinumab treatment (≤2.5 years in the open-label extension ECZTEND and ≤1 year in PTs).
  - ECZTRA 1/2: double-blinded, randomized, placebo-controlled, 52-week monotherapy trials
  - ECZTRA 3: double-blinded, randomized, placebo-controlled, 32-week TCS combination trial
  - ECZTRA 4: open-label, 14-week, drug-drug interaction (DDI) trial
  - ECZTRA 5: double-blinded, randomized, placebo-controlled, 16-week, vaccine antibody-response trial
  - ECZTRA 7: randomized, double-blinded, placebo-controlled, 26-week TCS combination trial in Cyclosporin A (CsA) refractory patients
- The interim analysis of IGA 0/1 and EASI-75 at Week 104 of ECZTEND included 616 patients (Week 104 cohort) **(Figure 1C)**

Patients and treatment

- Patients were eligible for ECZTEND regardless of prior treatment group or response in PT
- **Key inclusion criteria:**
  - Completion of the treatment period(s) in one of the PTs (ECZTRA 1–8 and TraSki IIS)
  - Compliance with the clinical trial protocol in the PT to the satisfaction of the investigator
  - Ability and willingness to self-administer tralokinumab treatment (or have it administered by a caregiver) at home after the initial three injection visits at the trial site (in this trial)
- **Key exclusion criteria:**
  - Last investigational medicinal product injection in the PT received >26 weeks prior to baseline
  - Development of a serious adverse event (SAE) deemed related to tralokinumab by the investigator in the PT, which in the opinion of the investigator, could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject
  - Development of an adverse event (AE) that was deemed related to tralokinumab by the investigator in the PT and led to temporary discontinuation of trial treatment, which in the opinion of the investigator, could indicate that continued treatment with tralokinumab may present an unreasonable safety risk for the subject
  - Treatment with:
    - Any biologic therapy/investigational biologic agent within specified period prior to baseline
    - Systemic immunosuppressive/immunomodulating drugs or systemic corticosteroids within five half-lives prior to baseline
    - Topical phosphodiesterase-4 inhibitors or topical Janus kinase inhibitors within 2 weeks prior to baseline
    - History of a clinically significant infection within 4 weeks prior to baseline

Figure 1. A. Patient recruitment from parent trials **B.** ECZTEND study design **C.** patient cohorts in ECZTEND interim analysis



[a]ECZTRA 7 is a trial in adult patients with severe atopic dermatitis who are not adequately controlled with or have contraindications to oral cyclosporine. [b]Patients received an initial loading dose of tralokinumab 600 mg, except for patients entering from ECZTRA 6. [c]After May 2021, some site visits will be replaced by telephone visits.
Abbreviations: AD, atopic dermatitis; ADA, anti-drug antibodies; adj., adjusted; AE, adverse event; CDLQI, Children's Dermatology Life Quality Index; CsA, cyclosporine; DDI, drug-drug interaction; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, EuroQol 5-Dimension Health Questionnaire 5-Level; FPFV, first patient first visit; IGA, Investigator's Global Assessment; IIS, investigator-initiated study; IL, interleukin; IMP, investigational medicinal product; IQR, interquartile range; LPLV, last patient last visit; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; PT, parent trial; PYE, patient-years exposure; q2w, every 2 weeks; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; SFU, safety follow-up; TCS, topical corticosteroids; TEAEs, treatment emergent adverse events.

Endpoints

- The primary endpoint of ECZTEND is the number of AEs during the treatment period from baseline of ECZTEND up to Week 268
- Secondary endpoints are the proportions of patients achieving an Investigator's Global Assessment (IGA) score of 0/1 (clear/almost clear) and >75% improvement in Eczema Area and Severity Index (EASI-75) at Weeks 16, 56, 88, 104, 136, 152, 184, 216, and 248
  - EASI-75 was calculated based on baseline EASI score in the PT; this is not applicable for patients from the TraSki IIS PT as these data will not be transferred to LEO Pharma

Statistical analyses

- AEs were coded over the course of the trial according to the Medical Dictionary for Regulatory Activities (MedDRA)
- All AEs described were treatment-emergent adverse events (TEAEs), defined as AEs reported after the first dosing of the study drug
- A summary of the number of AEs, the rate of AEs, the number (percentage) of patients with any TEAEs, deaths, SAEs, withdrawals from the trial due to AEs, treatment-related AEs, and severe AEs are presented
- Event rates are presented as the number of events per 100 patient-years of exposure (PYE)

Results

Patient characteristics

- This interim safety analysis included 1442 patients from the PTs ECZTRA 1, 2, 3, 4, 5, and 7 who had received ≥1 dose of tralokinumab at data cut-off, April 30, 2021 **(Table 1)**
  - Slightly more patients were male (57.6%), median age was 38.0 years (interquartile range [IQR] 27.0–50.0), and median age at onset of atopic dermatitis was 3.0 years (IQR 1.0–15.0) **(Table 1)**

Table 1. ECZTEND interim analysis baseline demographic and disease characteristics

Baseline Demographics	ECZTEND interim safety analysis set n=1442	
Age, Median years (IQR)	38.0 (27.0; 50.0)	
Sex, n (%)		
Male	831 (57.6)	
Female	611 (42.4)	
Race, n (%)		
White	1093 (75.9)	
Black	108 (7.5)	
Asian	203 (14.1)	
Parent trial, n (%)		
ECZTRA 1	450 (31.2)	
ECZTRA 2	293 (20.3)	
ECZTRA 3	282 (19.6)	
ECZTRA 4	31 (2.1)	
ECZTRA 5	149 (10.3)	
ECZTRA 7	237 (16.4)	
Age at onset of AD, median years (IQR)	3.0 (1.0; 15.0)	
Duration of AD, median years (IQR)	27.0 (18.0; 39.0)	
Disease Characteristics	**Parent Trial Baseline**	**ECZTEND Baseline**
IGA severity, n (%)		
Clear/minimal (score=0/1)	-	442 (30.6)
Mild (score=2)	-	524 (36.3)
Moderate (score=3)	765 (53.1)	391 (27.1)
Severe (score=4)	677 (46.9)	85 (5.9)
EASI, median (IQR)	26.8 (20.5; 37.6	4.8 (1.7; 12.0)
SCORAD, median (IQR)	67.7 (60.0; 77.9)	30.2 (18.7; 45.0)
DLQI, median (IQR) n	16.0 (11.0; 22.0) 1391	5.0 (2.0; 10.0) 1400
Worst weekly pruritus NRS[b], median (IQR) n	7.9 (6.8; 8.8) 1257	5.0 (3.0; 7.0) 1440

[a]Available in 1440 patients. [b]In PTs, worst sleep/pruritus NRS is assessed daily; in ECZTEND, worst sleep/pruritus NRS is assessed based on recall of the previous week before the visit.

- Median duration of atopic dermatitis was 27.0 years (IQR 18.0–39.0) and median body surface area affected at parent-trial baseline was 46.0% (IQR 31.0–68.0) **(Table 1)**
- Most patients were recruited from Europe (54.9%) and North America (39.2%)
- Median time from last dose in PT to first dose in ECZTEND was 34.0 days (IQR 14.0–80.0)
- Patients had up to 42 months of tralokinumab exposure with a median total time on tralokinumab (including PTs plus ECZTEND) of 131.5 weeks (IQR 83.4–161.8) at the time of data cut-off
- A total of 330 (22.9%) patients permanently discontinued the ECZTEND trial
  - The most common reasons for discontinuation were lack of efficacy (5.5%), other reasons (5.2%), and withdrawal by patient (3.4%)

Summary of AEs in ECZTEND

- In the 1442 patients exposed to tralokinumab in ECZTEND, the total exposure time was 2446.2 PYE
- Tralokinumab was well-tolerated in the ECZTEND interim safety analysis set, with an overall safety profile comparable to that of the initial treatment period in the PTs
- Overall, 1127 patients reported experiencing an AE (78.2%), with 101 patients reporting serious AEs (7.0%) **(Table 2)**
- The majority of AEs were of mild severity, at 66.3%
- AEs led to withdrawal from ECZTEND in 34 patients
  - Of these AEs, 8 were AD, 2 were cancer, 2 invasive ductal breast carcinoma, 2 prostate cancer, 2 conjunctivitis, and 2 allergic conjunctivitis
  - All other events were reported as single events without clustering on any type of AE

Most frequent AEs and AEs of interest

- The most frequent AEs (≥5% by MedDRA preferred term) were viral upper respiratory tract infection (mainly reported as common cold-related symptoms), atopic dermatitis, upper respiratory tract infection, headache, and conjunctivitis **(Table 3)**
- In addition, 2.5% of patients reported injection site reaction, 2 patients (0.1%) reported eosinophilia, 38 (2.6%) reported herpes simplex, and 30 (2.1%) reported herpes zoster.
- Overall, the pattern of frequently reported AEs in ECZTEND was similar to that observed with tralokinumab in the PTs
- Serious AEs (SAEs) are summarized in **Table 4**
- Most SAEs were reported as single events without any clustering on type of SAE
- Serious infections and infestations reported in more than one patient were corona virus infection, eczema herpeticum, and tonsillitis
- The number of malignancies reported was 7 (excluding non-melanoma skin cancer), with no type of malignancy repeated in more than 2 patients
- No events of conjunctivitis were SAEs
- No deaths were reported

Table 2. Summary of AEs in ECZTEND at the April 30, 2021, data cut-off (safety analysis set)

	AEs in ECZTEND interim safety analysis set		AEs Week 12-16 in parent trials[a]			
	Tralokinumab Q2W + optional TCS (n=1442; PYE=2446.2)		Tralokinumab Q2W ± TCS (n=1605; PYE=473.2)		Placebo Q2W ± TCS (n=680; PYE=193.1)	
	n (%)	Rate[b] (nP/100 PYE)	n (adj. %)	Rate (nP/100 PYE)	n (adj. %)	Rate (nP/100 PYE)
All AEs	1127 (78.2)	198.7	1080 (65.7)	639.5	449 (67.2)	678.3
Severity						
Mild	956 (66.3)	132.6	881 (53.2)	429.8	326 (49.0)	391.0
Moderate	628 (43.6)	59.5	518 (31.5)	189.5	258 (39.0)	254.3
Severe	102 (7.1)	6.6	77 (4.6)	20.2	40 (6.3)	33.0
Serious AEs	101 (7.0)	4.9	37 (2.1)	7.4	18 (2.8)	11.9
AEs leading to drug withdrawal	34 (2.4)	1.4	38 (2.3)	9.9	20 (2.8)	13.3
Outcome						
Not recovered/not resolved	378 (26.2)	24.9	232 (14.3)	65.4	90 (13.5)	65.2
Recovering/resolving	190 (13.2)	11.0	79 (5.0)	18.9	36 (5.4)	22.7
Recovered/resolved	1052 (73.0)	160.1	997 (60.2)	544.5	416 (62.4)	585.4
Recovered/resolved with sequelae	20 (1.4)	0.9	18 (1.0)	3.5	2 (0.3)	1.7
Unknown	32 (2.2)	1.6	27 (1.7)	7.0	6 (0.9)	3.3

[a]Pooled safety analysis set includes patients from parent trials ECZTRA 1, 2, 3, 5, and Phase 2b. [b]Rate calculated by number of AEs divided by PYE, multiplied by 100. As ECZTEND is an ongoing study, the percentage of AEs not recovered/not resolved is likely to change.
%, percentage of patients with ≥1 event; adj., adjusted; AE, adverse event; n, number of patients with ≥1 event; PYE, patient-years of exposure; Q2W, every 2 weeks; TCS, topical corticosteroids.

Control of AD signs and symptoms in patients with 104 weeks in ECZTEND (n=616)

- In patients who reached the 2-year time point (Week 104), or would have reached that time point had they not discontinued earlier, prior to data cutoff April 30, 2021:
  - EASI-75 was achieved by 77.6% of patients, by modified NRI
  - IGA 0/1 was achieved by 46.4% of patients, by modified NRI
- NRS ≤3 was achieved by 54.4% of patients and DLQI ≤5 was achieved by 68.8% of patients, by modified NRI

Limitations

- The safety analyses presented here do not capture AEs that may have occurred during the PTs
- An analysis of the full patient exposure from PT will be reported in the future

Table 3. Summary of most frequently reported AEs (≥5.0% of patients)

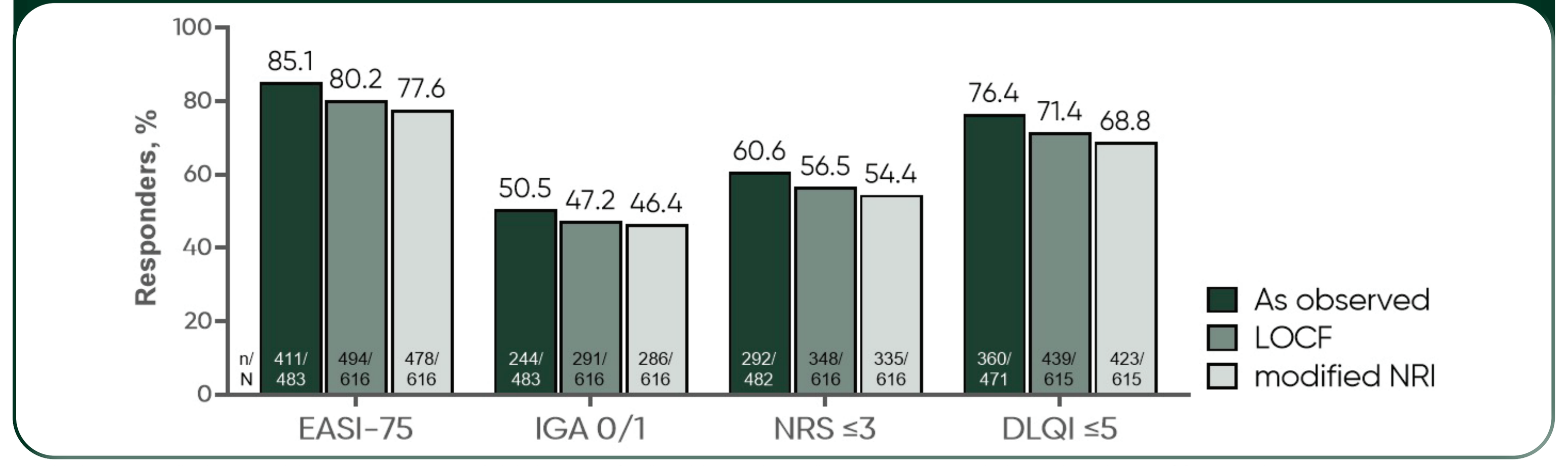
	AEs in ECZTEND interim safety analysis set		AEs Week 12-16 in parent trials[a]			
	Tralokinumab Q2W + optional TCS (n=1442; PYE=2446.2)		Tralokinumab Q2W ± TCS (n=1605; PYE=473.2)		Placebo Q2W ± TCS (n=680; PYE=193.1)	
	n (%)	Rate[b] (nP/100 PYE)	n (adj. %)	Rate (nP/100 PYE)	n (adj. %)	Rate (nP/100 PYE)
Viral upper respiratory tract infection[c]	295 (20.5)	18.2	256 (15.7)	65.1	78 (12.2)	51.3
Dermatitis atopic	257 (17.8)	17.9	272 (15.4)	68.0	167 (26.2)	139.7
Upper respiratory tract infection	101 (7.0)	5.8	92 (5.6)	20.8	33 (4.8)	18.5
Headache	79 (5.5)	4.4	72 (4.6)	21.6	26 (3.9)	19.6
Conjunctivitis	77 (5.3)	3.8	90 (5.4)	21.0	13 (1.9)	6.9

[a]Pooled safety analysis set includes patients from parent trials ECZTRA 1, 2, 3, 5, and Phase 2b. [b]Rate calculated by number of AEs divided by PYE, multiplied by 100. [c]Most commonly reported as common cold.

Table 4. Summary of serious AEs by Preferred Type (>0.1% of patients)

	SAEs in ECZTEND interim safety analysis set	
	Tralokinumab Q2W (n=1442; PYE=2446.2)	
	n (%)	Rate (nE/100 PYE)
Serious AEs (all)	101 (7.0)	4.9
Dermatitis atopic	6 (0.4)	0.2
Asthma	3 (0.2)	0.1
Corona virus infection	3 (0.2)	0.1
Eczema herpeticum	3 (0.2)	0.1

Figure 2. Proportion of patients with 104 weeks in ECZTEND prior to data cutoff achieving EASI-75, IGA 0/1, Worst Weekly Pruritus NRS ≤3, and DLQI ≤5



Data is relative to baseline in parent trial, n=616. The observed analysis includes data for all participants with a valid measurement at the indicated timepoint. The LOCF method imputes the value recorded at the participant's last visit for subsequent missed timepoints. The modified NRI method considers participants who discontinue from trial due to adverse event(s) or lack of efficacy as non-responders, and other missing are imputed with LOCF.

Conclusions

- This interim analysis of ECZTEND demonstrates that long-term use of tralokinumab 300 mg Q2W was well-tolerated, and no new safety signals were identified with up to 42 months of treatment
- Overall, tralokinumab 300 mg Q2W plus optional TCS demonstrated sustained long-term improvement in extent and severity of atopic dermatitis at Week 104
- This analysis confirms the long-term benefit-risk profile of targeted IL-13 inhibition with tralokinumab in patients with moderate-to-severe AD

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Disclosures

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